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STATEMENT FOR THE RECORD

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BEFORE THE
SUBCOMMITTEE ON HEALTH AND ENVIRONMENT
COMMITTEE ON COMMERCE
UNITED STATES HOUSE OF REPRESENTATIVES

FEBRUARY 12, 1998

I am Harold Varmus, Director of the National Institutes of Health. My statement addresses how somatic cell nuclear transfer offers potential benefits for medical research and medical practice. This technology was first brought to public attention when Ian Wilmut and his colleagues at the Roslin Institute, Edinburgh, published in the February 27, 1997 issue of *Nature*, the results of their cloning experiments in sheep. The likely benefits from these studies are contributions to animal husbandry and medical research. But the importance of these contributions has been dwarfed by the public's fascination with Dolly, a lamb cloned from the cell of an adult sheep. The successful cloning of an adult sheep sharply focused public attention on the possibility of cloning a human being.

The President, recognizing the ethical and societal implications of the Dolly experiment, requested the National Bioethics Advisory Committee to examine this issue and report recommendations within 90 days. The Committee concluded "that there should be imposed a period of time in which no attempt is made to create a child using somatic cell nuclear transfer." They further cautioned that "Any regulatory or legislative actions undertaken to effect the foregoing prohibition on creating a child by somatic cell nuclear transfer should be carefully written so as not to interfere with other important areas of scientific research." Their final suggestion was to formally re-evaluate this issue in three to five years. Subsequently, over 67,000 scientists involved in reproduction biology signed a voluntary moratorium on the cloning of a human.

This hearing is a continuation of the public discourse on this issue. It is imperative that this discourse be informed and comprehensive. I would like to discuss briefly the science that was used to create Dolly, and describe the scientific and medical promises of this technology.

SOMATIC CELL NUCLEAR TRANSFER–WHAT IS IT?

I am certain that many people have heard of somatic cell nuclear transfer. I am also certain that there is much confusion and misunderstanding about this technology.

In order to understand this technology, it is necessary to briefly review normal sexual reproduction in mammals (see the top of Chart 1). Normally, an egg and sperm join to create a fertilized egg which develops into an embryo and ultimately a newborn animal. In this situation, the progeny receives genetic material from both the mother and father.

In the Dolly experiment, a lamb was produced using the technology of somatic cell nuclear transfer. Unlike the normal process of sexual reproduction in which an egg and a sperm each contribute genetic material, somatic cell nuclear transfer is asexual. A somatic cell is any cell except the egg cells or sperm cells. Somatic cells contain the full complement of chromosomes. In contrast, an egg or a sperm contains half that number.

Somatic cell nuclear transfer is done in the following way (see the bottom of Chart 1), using sheep as an example. First a normal sheep egg cell is taken from a ewe and the nucleus (the cell structure containing the chromosomes) is removed, yielding an egg cell containing the nutrients

and other energy producing materials that are essential for embryo development, but not the chromosomes. Next, a somatic cell is isolated--in the case of Dolly, a cell grown in cell culture from the mammary tissue of an adult sheep. Under certain conditions, the somatic cell (in this example, the mammary cell) is placed next to the egg from which the nucleus had been removed, an electrical stimulus is applied, and the two cells fuse. The result is a cell that contains the nutrient environment of an egg cell and genetic material only from the donated somatic cell. This is not sexual reproduction, since genetic material is derived from only one, not two, individuals. There is no sperm involved. The egg provides only the environment for growth. After a number of cell divisions, these cells are placed into the uterus of a sheep. In the case of Dolly, a lamb was born -- an identical twin of the original donor, only born later.

The birth of a lamb cloned from an adult sheep was dramatic. But we must interpret the results cautiously because only one successful experiment of this type has been reported. In fact, Dolly was the only success among 276 failed attempts. Before somatic cell nuclear transfer could even be considered as a technique for animal reproduction, there are a number of scientific hurdles that would have to be addressed. First, the Dolly experiment needs to be repeated; in fact it needs to be repeated many times, with other types of somatic cells, with other animals, and under different conditions.

POTENTIAL BENEFITS FROM SOMATIC CELL NUCLEAR TRANSFER TECHNOLOGY

The interest of the scientific world focuses on somatic cell nuclear transfer as a technology for animal husbandry and for medical research. Let me describe the reasons for this. The experiment

that created Dolly demonstrated that, when appropriately manipulated and exposed to the correct environment, the genetic material of somatic cells could regain their full potential or totipotent status. These asexually produced totipotent cells (APT cells (see Chart 2)) were *totally potent* in that they had the capacity to form any type of cell in the body - a muscle cell, a liver cell, a blood cell. At the appropriate time, these APT cells began to specialize into specific types of cells; this process was triggered when specific genes are turned on or off.

It had long been thought that the process of cell specialization was strictly a one way street, and that a specialized adult cell could not resume a highly immature state, but this dogma was challenged by the experiment that produced Dolly. Medical researchers realized that if the genetic material of a specialized somatic cell could be stimulated to return to a totipotent state, with the potential to become any kind of cell, the potential uses of this technology for the study and treatment of disease were remarkable. Today, investigators are focused on the idea of creating cells and tissues for transplantation and research. They are not focused on cloning a human. Researchers are working to understand how different genes are turned on and off. Once this is known, it might be possible to take totipotent cells and direct them to specialize into a specific type of cell, for example a heart, liver, or a muscle cell. These cells could then be used for cell and tissue transplantation.

Somatic cell nuclear transfer research offers the potential for developing individualized cell and tissue therapies that *cannot* be developed using current methods. Medical practitioners and researchers are currently transplanting cells to replace damaged or diseased cells in humans. But

these procedures require a donor from whom cells can be taken. With the exception of cells from an identical twin, donor cells are genetically different from the recipient (top of Chart 2). When they are placed into the patient, the patient's immune system sees these cells as foreign and tries to reject them from the body. In order to prevent this rejection, drugs are used to suppress the normal immune response. Unfortunately, these drugs are not always effective for preventing rejection, and they have serious toxicities including malignancy and even death. An additional problem with transplant medicine is the shortage of human donors; the supply of replacement cells and tissue is inadequate.

Somatic cell nuclear transfer could overcome many of these obstacles. Using this technology, a patient's own cells from any part of the body could be used to generate the needed therapeutic cells or tissue in adequate amounts. Because these cells would be a genetic match, rejection should not occur and the need for anti-rejection drugs would be minimal. Treatment could be revolutionized for patients with diseases such as diabetes, leukemia, heart disease, cancers and liver disease, to name a few. Such treatments might be limited to diseases or disorders that do not have a major genetic component, for the transplanted cells would contain the same genes as the failing cells they are intended to replace.

Somatic cell nuclear transfer technology also holds hope for patients with neurologic injury and disease. Because mature, specialized nerve cells do not reproduce, it has been virtually impossible to create cultures of replicating nerve cells. If with somatic cell nuclear transfer we were able to take a totipotent cell and direct it to produce different types of nerve cells, this might be a major

breakthrough for patients with spinal cord injury, Parkinson's disease, Lou Gehrig's disease, multiple sclerosis or Alzheimer's disease.

Animal Cloning

It is important not to lose sight of the original motivation for the Dolly experiment. The most direct and immediate benefit of somatic cell nuclear transfer is animal cloning, the genetic duplication of an animal. In traditional breeding practices, the offspring of an animal are sexually reproduced from genetically different parents and, therefore, may not share all of the characteristics that made the parents valuable. In conventional breeding, it takes years to produce many animals with similar genetic characteristics. Cloning could speed up this process and could allow the production of genetically identical animals.

This technique would be particularly valuable for research. The use of genetically identical animals could dramatically reduce the numbers of animals needed for experiments. For the first time, researchers could be sure that differences in responses to drugs and other interventions are due to the interventions, not to genetic differences among animals.

Cloning could also contribute to animal husbandry and medical research by facilitating transgenic technology. A transgenic animal is one that is genetically altered by inserting a new gene with the desired attributes into the DNA of a fertilized egg. Transgenic animals are valuable for a number of reasons. They can be engineered to have decreased susceptibility to bacterial infection, to have increased milk production, and to produce pharmaceutically important proteins in their milk.

Recently, calves were cloned with the gene that enabled them to produce human clotting factors in their milk for the treatment of hemophilia. Cloning the animal that incorporated the gene of interest would be much faster than selective breeding and would decrease the amount of time required to produce transgenic animals. Future advances may also allow the development of animal clones with tissues and organs that are compatible for human transplantation purposes.

CONCLUSION

Somatic cell nuclear transfer holds great potential for animal husbandry and medical research and these possibilities can be accomplished without using this technology to create a human being. On June 9, 1997 the President transmitted to Congress legislation making it illegal for anyone to create a human being through cloning. The Administration believes that using somatic cell nuclear transfer cloning techniques to create a human being is untested, unsafe, and morally unacceptable. Legislation banning the creation of the human being using cloning technology must strike a careful balance: to ban the creation of a human being without impeding promising research requiring the use of the cloning technology.

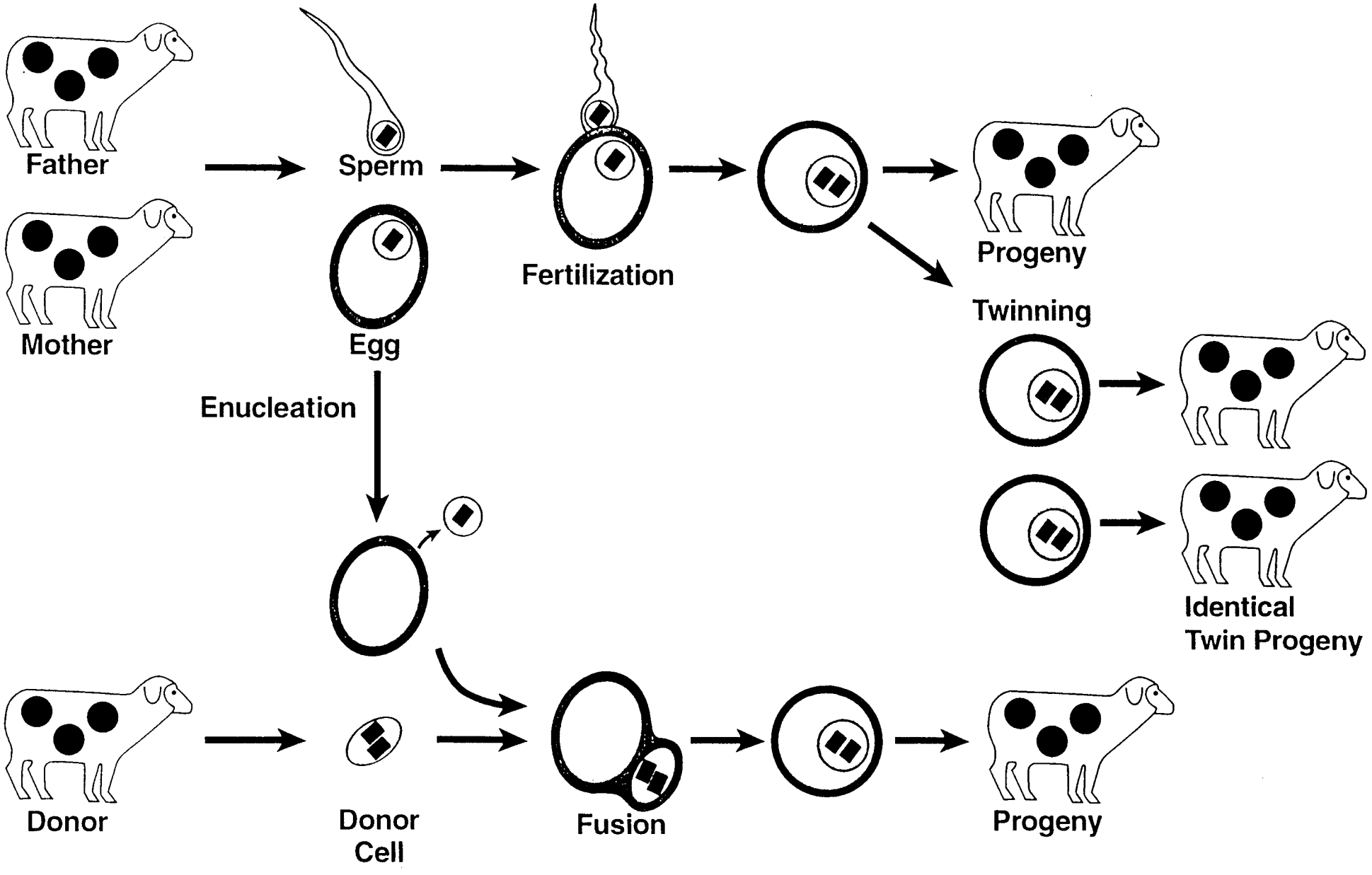
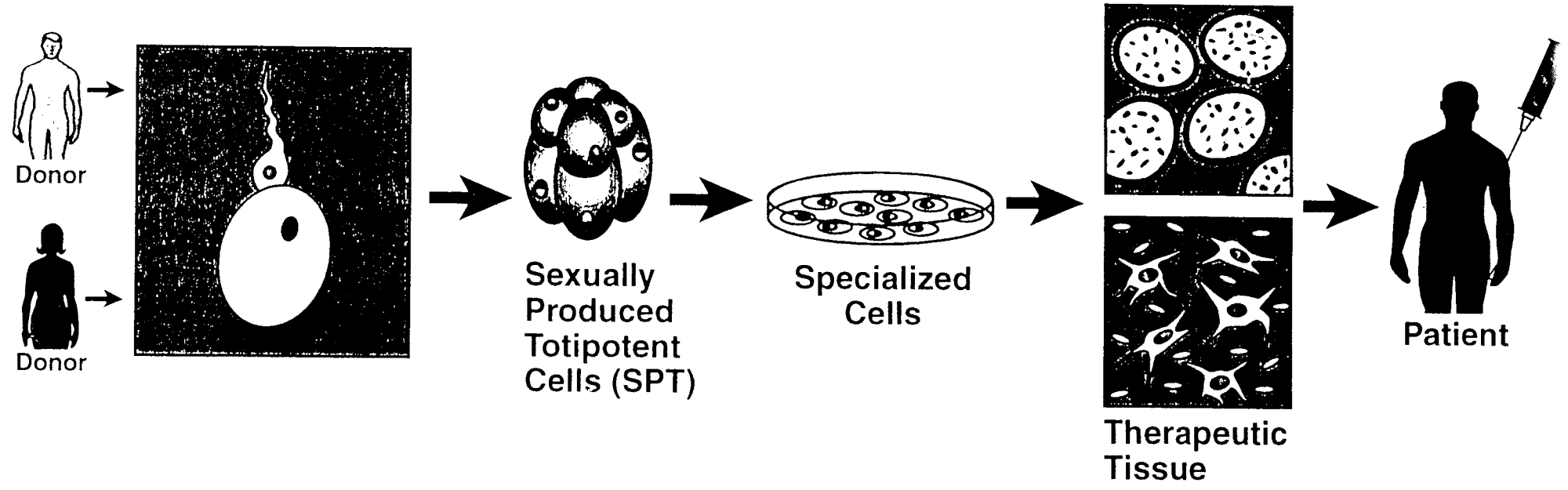

Father
Mother
Sperm
Egg
Fertilization
Progeny
Twinning
Enucleation
Identical
Twin Progeny
Donor
Donor
Cell
Fusion
Progeny

CHART 7


Donor
Donor
Sexually
Produced
Totipotent
Cells (SPT)
Specialized
Cells
Therapeutic
Tissue
Patient

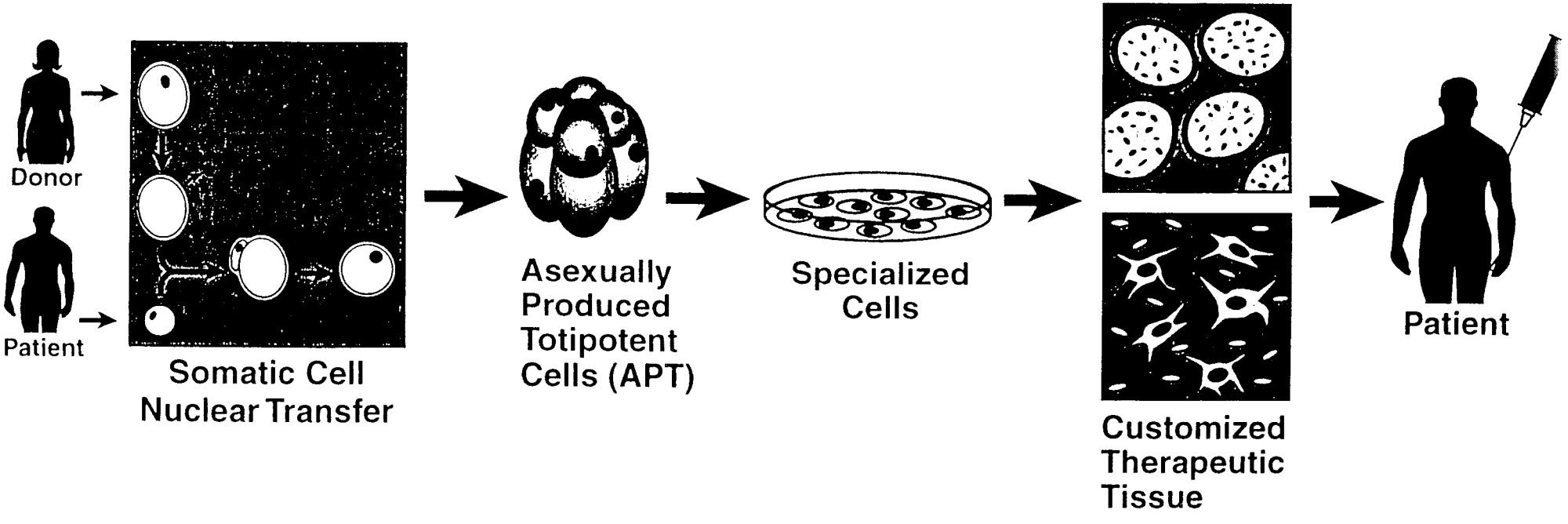

Donor
Patient
Somatic Cell
Nuclear Transfer
Asexually
Produced
Totipotent
Cells (APT)
Specialized
Cells
Customized
Therapeutic
Tissue
Patient

CHART 2